REMARKS

Status of the claims

Claims 1-27 have been cancelled. New claims 28-45 have been added. Support for these claims can be found throughout the specification *inter alia* as follows:

claim 28 - page 4 lines 10-11 and 26-29; page 5, lines 3-4; page 6, lines 5- 14; and page 8 lines 3-5

claims 29 and 30 - page 30, lines 22-23

claim 31 - page 6, lines 12-14

claims 32-34 - page 4, lines 27-30

claim 35 - page 6, lines 7-13

claim 36 - page 14, Table 2 and lines 5-12

claim 37 - page 8, lines 15-16

claim 38 - page 5, lines 12-13

claims 39 and 40 - page 8, lines 1-3

claims 41 and 42 - page 8, lines 18-25

claim 43 - page 15, lines 4-6

claim 44 -page 6, lines12-14

claim 45 - page 16 lines 6-9.

With respect to all cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

The amendments to the claims are to clarify the nature of the subject matter claimed.

I. Rejection under 35 U.S.C. § 112

Claim 7 was rejected under 35 U.s.c. § 112 ¶ 2 as indefinite for using the abbreviations "CFTR" and "GALT". This rejection is moot since claim 7 has been cancelled, and new claim 34 defines the terms before the recitation of the abbreviations.

II. Rejection under 35 U.S.C. § 102b

Claims 1, 8, 9, 12, 14, 17, 18, 21 and 24 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Lashkari et al. (Proc. Natl. Acad. Sci. USA, 1997, 94:13057-13062). Claims 1, 8, 9, 12, 14, 17, 18, 21 and 24 have been cancelled. This rejection is traversed with respect to the cancelled claims, however that point is moot. The new claims are also not anticipated by Lashkari since this reference does not teach all of the limitations of claim 28, and of the claims that depend from claim 28.

The method of claim 28 is a method of simultaneously genotyping multiple samples in a single round of hybridization. The method comprises incubating a microarray of polynucleotide samples with a mixture of oligonucleotides of *known* sequence. The microarray contains a plurality of classes of polynucleotides with each class of polynucleotides in a distinct location. Each class of polynucleotides has polynucleotides with a defined segment containing a marker selected from a marker for a gene and markers for one or more allelic variants of the gene. The oligonucleotides in the mixture consist essentially of optionally hybridization control oligonucleotides, and of oligonucleotides having sequences complementary to the defined segments containing markers, for each class of polynucleotides for which a genotype is to be determined. The oligonucleotides in the mixture that are complementary to a class of polynucleotides are selected from those with sequences complementary to (1) a defined segment of a gene, (2) defined segments of one or more allelic variants of the gene, and (3) a defined segment of a gene and defined segments of one or more allelic variants of the gene. The incubating allows the formation of hybrids comprised of polynucleotides of the array and complementary oligonucleotides of the mixture, and allows discrimination at single nucleotide resolution. The method also comprises detecting stable hybrids formed during the incubation (if

any), wherein the formation of a hybrid or lack of formation of a hybrid after a single round of hybridization is indicative of a genotype.

All elements of the new claims 28 (and its dependent claims) are not taught by the Lashkari reference. For example, Lashkari does not teach the use of oligonucleotides of known sequences as probes for the microarray. Instead, Lashkari teaches that the probes for hybridization to the microarray are preparations of cDNA prepared from total mRNA, or genomic DNA. (Page 13058, column 2). This clearly would generate a mixture of probes with largely unknown sequences, and not a mixture of oligonucleotides of known sequence.

In addition, for example, the Lashkari method would not allow discrimination at single nucleotide resolution. Lashkari teaches that the published method does not detect small intragenic deletions, but rather it detects large deletion polymorphisms. (Page 13059, column 2, last paragraph).

In view of this, Lashkari cannot anticipate the Applicant's claimed methods since at least two limitations of the claims are not met. Therefore, Applicant respectfully requests withdrawal of this rejection.

III. Rejections under 35 U.S.C. § 102(b)/103(a)

Claims 1, 5, 8, 11, 12, 14, 17, 18, 21, 24 and 26 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as allegedly obvious over Brown et al. (U.S. Patent No. 5,807,522, issued September 15, 1998).

Claims 1-26 have been canceled. New claim 28 and its dependent claims are neither anticipated nor made obvious by the Brown '522 patent.

Applicant's method of claim 28 hybridizes probe oligonucleotides of known sequence with the plurality of polynucleotides on the microarray that are to be genotyped. The mixture of probe oligonucleotides consist essentially of oligonucleotides having sequences complementary to defined segments (containing markers) for each class of polynucleotides for which a genotype is to be determined, and optionally oligonucleotides for controls.

Brown does not teach these elements of the claim. Brown teaches generally, that the probes for the microarrays are mixtures of labelled cDNAs that are prepared from total mRNA (Column 4, lines 52-64).

In Example 1 Brown teaches probe mixtures prepared by a method using random primers and pooled chromosomal DNA. These probe mixtures would not be a mixture of oligonucleotides of known sequence.

In Example 1 Brown also teaches that individual clones or pools of clones can be used to generate a probe mixture. In Example 2, Brown teaches the use of cDNA prepared from total mRNA as a probe. In Example 3, Brown teaches hybridization of the different yeast DNAs from 192 clones with a single oligonucleotide per quadrant. None of these methods meet the limitations of claim 28. None of these probe mixtures consist essentially of oligonucleotides having sequences complementary to defined segments (containing markers) for each class of polynucleotides on the microarray for which a genotype is to be determined.

Moreover, there is no suggestion or motivation in the Brown reference that leads to Applicant's claimed invention. There is no teaching in Brown that in genotyping multiple samples, the microarray containing a plurality of classes of polynucleotides is to be probed with a defined *mixture* of oligonucleotides of *known* sequence. Instead, Brown teaches that in genotyping studies the arrays containing gene segments are to be probed with complex mixtures of largely unknown composition (e.g. cDNA from total mRNA or total DNA from a patient)('522 patent, column 14, line 55 to column 15, line 4). Alternatively, Brown teaches that the array contains a single patient's or organism's DNA, and that is probed with a single mutated allele or mutated marker (Column 15, lines 47).

All of the claims that depend from claim 28 contain the same limitations as claim 28. Therefore, Applicant respectfully submits that claim 28 and its dependent claims are patentable in view of Brown.

IV. Rejections under 35 U.S.C. § 103(a)

A. Claims 3, 4, 6, 7, 9 and 10 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Brown et al. (U.S. Patent No. 5,807,522, issued September 15, 1998).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. See *In re Royka*, 490 F.2d 981 (CCPA 1974); MPEP 2143.03. In addition, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine,* 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); MPEP 2143.01. The mere fact that references can be modified or even that the modification to the claimed invention is well within the capabilities of one of ordinary skill in the art is not sufficient to establish *prima facie* obviousness. See *In re Mills,* 916 F.rd 680, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP 2143.01.

Applicants submit that the Office Action fails to show how the sole Brown et al. reference cited in the rejection of claims 3, 4, 6, 7, 9, and 10 discloses or suggests every limitation of the rejected claims. Claims 3, 4, 6, 7, 9, and 10 have been canceled. New claim 28 and its dependent claims with respect to the Brown reference have been discussed in Section III, where it is shown that certain limitations in the claim are neither taught nor suggested by the Brown reference. Therefore, Applicant respectfully submits that claim 28 and its dependent claims are patentable in view of Brown.

B. Claims 13, 15, 16 and 25 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Brown et al. (U.S. Patent 5,807,522, issued September 15, 1998) in view of Wang et al. (Science, 1998, 280:1077-1082).

Claims 13, 15, 16, and 25 have been cancelled. Claim 28 is distinct from the teachings of Brown. There is no teaching or suggestion in the Brown reference to use as probes mixtures of oligonucleotides of known sequence (see Section III above). Wang teaches the use of hybridization of oligonucleotides probes on a chip with PCR products from STSs containing

random genomic sequence from a single individual (page 1077 column 3; page 1078, column 3, par. 2; and pg 1081 note 16). Thus, Wang does not add the missing elements of Applicant's claimed method. The combination of Wang and Brown does not teach that in genotyping multiple samples, the microarray containing a plurality of classes of polynucleotides to be genotyped is to be probed with a defined *mixture* of oligonucleotides of *known* sequence. Therefore, claim 28, is not obvious over Brown in combination with Wang.

Applicant respectfully submits that claim 28 and its dependent claims are patentable over Brown in view of Wang.

C. Claims 19, 20, 22 and 23 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Brown et al. (U.S. Patent No. 5,807,522, issued September 15, 1998) in view of Fodor et al. (U.S. Patent No. 5,800,992, filed June 25, 1996).

Claims 19, 20, 22 and 23 have been cancelled. Claim 28 is distinct from the teachings of Brown for the reasons discussed in Sections III and IV.A. The Fodor '992 patent teaches methods to prepare a substrate having a very high density matrix pattern of positionally defined specific recognition reagents on a solid surface. This system is used to probe a target molecule. (Column 6, lines 23 to 48). The '922 patent does not provide the missing elements of the Brown reference with respect to Applicant's claim 28. Thus, the combination of the cited references does not disclose all elements of the present invention.

Applicant respectfully submits that claim 28 and its dependent claims are patentable over Brown in view of Fodor.

New Grounds for Rejection

V. Rejections under 35 U.S.C. § 102 A. Claims 1, 3-5, 8-12, 14-17, 24, 26 and 27 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Drmanac (U.S. Patent No. 6,025,136, filed August 28, 1998). Applicants submit that the Office Action fails to show how

the sole Drmanac patent specifically points out every aspect of the present invention. Claims 1-27 are canceled. New claim 28 has elements that are not taught by the Drmanac patent.

Claim 28 specifies that the oligonucleotides in the probe mixture consist essentially of (with optional oligonucleotide controls), oligonucleotides having sequences complementary to the defined segments of the polynucleotides *for each class of polynucleotide* for which a genotype is to be determined. Applicant's method also specifies that the formation of a hybrid (or lack thereof) after a single round of hybridization is indicative of the genotype.

By contrast, the Drmanac procedures use multiple hybridization cycles with each cycle using a set of probes that is underinclusive for the samples to be tested. *See* column 2, line 37 to line 61; column 7, line 29 to line 45. Thus, since Drmanac does not teach every element of Applicant's method it does not anticipate it, and Applicant respectfully submits that claim 28 and its dependent claims are patentable over Drmanac.

VI. Rejections under 35 U.S.C. § 103(a)

A. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Drmanac (U.S. Patent No. 6,025,136, filed August 28, 1997).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. See *In re Royka*, 490 F.2d 981 (CCPA 1974); MPEP 2143.03. In addition, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine,* 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); MPEP 2143.01. The mere fact that references can be modified or even that the modification to the claimed invention is well within the capabilities of one of ordinary skill in the art is not sufficient to establish *prima facie* obviousness. See *In re Mills,* 916 F.rd 680, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP 2143.01. As discussed above in Section V, Drmanac does not teach each and every limitation of Applicant's claimed invention, so this reference by

itself cannot make obvious Applicant's invention. Moreover, there is no suggestion in Drmanac to utilize a probe mixture with oligonucleotides consisting essentially of (with optional oligonucleotide controls), oligonucleotides having sequences complementary to the defined segments of the polynucleotides *for each class of polynucleotide* for which a genotype is to be determined such that the formation of a hybrid (or lack thereof) after a single round of hybridization is indicative of the genotype when a plurality of samples are to be genotyped. Thus, claim 28 and its dependent claims are not obvious in view of Drmanac.

B. Claims 13 and 25 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Drmanac (U.S. Patent No. 6,025,136, filed August 28, 1997) in view of Wang et al. (Science, 1998, 280:1077-1082). Claims 13 and 25 have been canceled. New Claim 28 contains elements not taught in Drmanac, as discussed in Section V, and does not suggest those elements, as discussed in Section VI A. Wang teaches the use of hybridization of oligonucleotides probes on a chip with PCR products from STSs containing random genomic sequence from a single individual (page 1077 column 3; page 1078, column 3, paragraph 2; and page 1081 note 16). Wang does not supply the elements missing from the Drmanac reference. Therefore, claim 28 and its dependent claims is not *prima facie* obvious in view of these references.

C. Claims 18-23 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Drmanac (U.S. Patent No. 6,025,136, filed August 28, 1997) in view of Fodor et al.. (U.S. Patent No. 5,800,992, filed June 25, 1996).

Claims 18-23 have been canceled. New Claim 28 contains elements not taught in Drmanac, as discussed in Section V, and does not suggest those elements, as discussed in Section VI A. Fodor et al. also does not teach or suggest the missing elements. The Fodor '992 patent teaches methods to prepare a substrate having a very high density matrix pattern of positionally defined specific recognition reagents on a solid surface. This system is used to probe a target molecule. (Column 6, lines 23 to 48). Fodor neither teaches nor suggests the elements missing

from the Dramanc reference. There is no suggestion in Fodor to utilize a probe mixture with oligonucleotides consisting essentially of (with optional oligonucleotide controls), oligonucleotides having sequences complementary to the defined segments of the polynucleotides *for each class of polynucleotide* for which a genotype is to be determined such that the formation of a hybrid (or lack thereof) after a single round of hybridization is indicative of the genotype when a plurality of samples are to be genotyped.

Applicant respectfully submits claim 28 and its dependent claims are not *prima facie* obvious in view of the cited references.

CONCLUSION

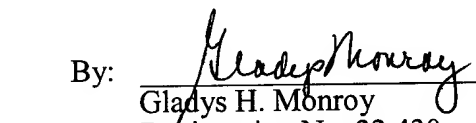
Applicants believe they have addressed all outstanding issues and that the claims are in condition for allowance, and an early Notice of Allowance is respectfully requested. The Examiner is encouraged to call the undersigned if she wishes to discuss any remaining issues or questions.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

In the unlikely event that the fee transmittal is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 529492000100.

Respectfully submitted,

Dated: August 15, 2002

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace the paragraph beginning on page 10, line 16 with the following:

Neonatal blood samples from 72 different newborns were isolated and amplified with gene-specific primers denoted ARDC100-109 in Table 1 below. These five primer pairs contain reactive amine groups corresponding to the C6 amino modifications from Glen Research (Sterling, VT), that allow specific attachment of the amplicons to microarray substrate. The "N" position in each oligonucleotide sequence in Table 1 below denotes the C6 amino modification. The primers pairs encompass five discrete genomic segments corresponding to a total of three human genes: ~~β-globin,~~ beta globin (β-globin), ~~CFTR and GALT~~ Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), and Galactose-1-phosphate uridyltransferase (GALT). The diseases associated with the β-globin, CFTR and GALT genes in human are Sickle Cell Anemia, Cystic Fibrosis and Galactosemia, respectively. The genomic segments encompassed five disease loci in the three genes and the approximate size of each amplicon was 60 base pairs. The total volume of each PCR reaction was 50 µl.

Please replace Table 1 beginning at page 11, line 13 with the following:

Table 1. PCR primers used to amplify genomic segments

Primer I.D.	Description	Sequence
ARDC-100	Sickle Cell C allele 5'	5' NAAACAGACACCATGGTG CAC 3' (SEQ ID NO:1)
ARDC-101	Sickle Cell C allele 3'	5' NCCCACAGGGCAGTAACGGCA 3' (SEQ ID NO:2)
ARDC-102	Sickle Cell E allele 5'	5' NGCAAGGTGAACGTGGATGAA 3' (SEQ ID NO:3)
ARDC-103	Sickle Cell E allele 3'	5' NGTAACCTTGATACCAACCTG 3' (SEQ ID NO:4)
ARDC-104	Cystic Fibrosis ΔF508 allele 5'	5' NCTGGCACCATTAAAGAAAAT 3' (SEQ ID NO:5)
ARDC-105	Cystic Fibrosis ΔF508 allele 3'	5' NTTCTGTATCTATATTCATCA 3' (SEQ ID NO:6)
ARDC-106	GALT Q188R 5'	5' NTGGGCTGTTCTAACCCCCAC 3' (SEQ ID NO:7)
ARDC-107	GALT Q188R 3'	5' NAACCCACTGGAGCCCCTGAC 3' (SEQ ID NO:8)
ARDC-108	GALT N314D 5'	5' NCCACAGGATCAGAGGCTGGG 3' (SEQ ID NO:9)

ARDC-109	GALT N314D 3'	5' NGGTAGTAATGAGCGTGCAGC 3' (SEQ ID NO:10)

Please replace Table 2, beginning at page 14, line 1 with the following:

Table 2. Mixtures of synthetic oligonucleotides

Mixture	Oligonucleotide I.D.	Oligonucleotide Sequence*
1	ARDC-110	3GACTCCTG(A/T)GGAGAA (SEQ ID NO:11)
	ARDC-111	5GACTCCTA(A/T)GGAGAA (SEQ ID NO:12)
	ARDC-112	5TGGTGGTGAGGCCCT (SEQ ID NO:13)
	ARDC-113	3TGGTGGTAAGGCCCT (SEQ ID NO:14)
	ARDC-114	3ATCATCTTTGGTGTT (SEQ ID NO:15)
	ARDC-115	5TATCATCGGTGTTTC (SEQ ID NO:16)
	ARDC-116	5CACTGCCAGGTAAGG (SEQ ID NO:17)
	ARDC-117	3CACTGCCGGGTAAGG (SEQ ID NO:18)
	ARDC-118	3CAACTGGAACCATTG (SEQ ID NO:19)
	ARDC-119	5CAACTGGGACCATTG (SEQ ID NO:20)
2	ARDC-125	BGACTCCTG(A/T)GGAGAA (SEQ ID NO:21)
	ARDC-126	BTGGTGGTAAGGCCCT (SEQ ID NO:22)
	ARDC-127	BATCATCTTTGGTGTT (SEQ ID NO:23)
	ARDC-128	BCACTGCCGGGTAAGG (SEQ ID NO:24)
	ARDC-129	BCAACTGGAACCATTG (SEQ ID NO:25)
	ARDC-135	DGACTCCTA(A/T)GGAGAA (SEQ ID NO:26)
	ARDC-136	DTGGTGGTGAGGCCCT (SEQ ID NO:27)
	ARDC-137	DTATCATCGGTGTTTC (SEQ ID NO:28)
	ARDC-138	DCACTGCCAGGTAAGG (SEQ ID NO:29)
	ARDC-139	DCAACTGGGACCATTG (SEQ ID NO:30)

*All sequences shown are 5' to 3' from left to right. 3 denotes Cy3; 5 denotes Cy5; B denotes biotin; D denotes dinitrophenol.

In the Claims:

Claims 1-27 have been cancelled.

Claims 28-45 have been added.